Acute traumatic coagulopathy

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Purpose of review
Mortality from trauma remains a global public health challenge, with most preventable deaths due to bleeding. The recognition of acute traumatic coagulopathy as a distinct clinical entity characterized by early coagulation dysfunction, arising prior to medical intervention, has revolutionized trauma management over the last decade. The aim of this article is to review our current understanding of acute traumatic coagulopathy.

Recent findings
We focus on recent advances in the mechanistic understanding of acute traumatic coagulopathy, particularly the changes in coagulation factors, physiological anticoagulants, endothelial activation, fibrinolysis and platelet dysfunction. Evolving diagnostic and therapeutic approaches are discussed, including viscoelastic coagulation monitoring and the role of tranexamic acid and blood products.

Summary
Emphasis is now placed on early prevention, diagnosis, and aggressive initial treatment of coagulopathy and fibrinolysis with haemostatic blood products and tranexamic acid in addition to red cell units in order to reduce bleeding and improve clinical outcomes.

Keywords
acute traumatic coagulopathy, endothelial activation, fibrinolysis, hemostatic resuscitation, hypoperfusion, microparticles, platelet dysfunction, tranexamic acid, viscoelastic coagulation monitoring

INTRODUCTION

Mortality from trauma is a major global health issue, causing over 4 million deaths a year [1]. Most potentially preventable deaths are due to bleeding, especially in wartime, but immediate management has changed dramatically and improved outcome [2]. This article will focus on our current understanding of acute traumatic coagulopathy (ATC).

WHAT IS ACUTE TRAUMATIC COAGULOPATHY?

The past decade has seen an explosion of publications describing an entity variously termed 'acute traumatic coagulopathy' (ATC), 'acute coagulopathy of trauma shock', or 'trauma induced coagulopathy,' describing an early coagulopathy associated with high bleeding risk and poor outcomes (Table 1) [3–12]. There is uncertainty about the underlying pathophysiological mechanisms and whether traumatic injury induces a unique coagulopathy when compared with other forms of major haemorrhage (e.g., obstetric or vascular) because no comparative studies have been undertaken. Nevertheless, the recognition that early coagulation changes following trauma portend poor outcomes has radically altered trauma resuscitation and improved outcomes [13].

CLASSIFICATION AND NAMING OF TRAUMA-ASSOCIATED COAGULOPATHIES

There are different approaches to classifying ATC, including by timescale in which temporal phases are described. The first phase is an immediate activation of multiple haemostatic pathways, including fibrinolysis, in association with tissue injury. The second phase is due to therapy-related factors during

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KEY POINTS

- Traumatic injury generates an acute coagulopathy defined usually by a prolongation of the prothrombin time.

- ATC is associated with increased morbidity and mortality.

- The pathogenesis of ATC relates to excessive stimulation of fibrinolysis and coagulation, changes in platelet function, and generation of microparticles.

- We argue that the changes of ATC are not driven by aPC.

resuscitation, and postresuscitation there is an acute phase response leading to a prothrombotic state, predisposing to venous thromboembolism. In some patients, especially if resuscitated late or inadequately, disseminated intravascular coagulation (DIC) may ensue.

The concept of ATC stems from the recognition that a prolonged prothrombin time (PT) and/or activated partial thromboplastin time (APTT) at hospital admission, prior to resuscitation, is associated with a three-fold to four-fold higher mortality rate and is independently associated with increased transfusion requirements, organ injury, septic complication, and critical care length of stay [4]. This supports the rationale for giving traumatic coagulopathy a distinct

name to emphasize these clinically important associations. For the purposes of this review, the term ATC will be used.

THE CLINICAL RELEVANCE OF ACUTE TRAUMATIC COAGULOPATHY

The role of ATC in forcing change in trauma management cannot be overstated. Previously, patients were initially resuscitated with red cell concentrates, with attention being paid to coagulopathy later. Retrospective data from the US military and civilian institutions described improved outcomes in those administered fresh whole blood [13,14] or fresh frozen plasma, cryoprecipitate and platelets in combination with red blood cells and tranexamic acid (TXA), with limitation of colloid or crystalloid infusions [13,15–19]; a practice known as 'haemostatic resuscitation' [20]. It may be that current transfusion strategies can be improved to further improve survival after ATC [21], and the results of the randomized controlled trials are awaited [22]. In North America, the difficulty in managing ATC has sparked a renewed interest in whole blood for trauma resuscitation [23–26]. In contrast, in some European countries, fibrinogen and other factor concentrates have replaced fresh frozen plasma in the management of ATC [27]. The empiric evolution of divergent clinical practice underscores the need for a better mechanistic understanding of ATC and for more clinical research.

Table 1. Suggested definitions and prevalence of acute traumatic coagulopathy

Study	Number of included patients	Definition of ATC	Average ISS	% penetrating injury	Time to blood sample	% of patients with ATC		
Brohi et al., 2003 [4]	1088	PT, APTT, TT >1.5x ULN	20[a]	25	73 min		24.4	
Macleod et al., 2003 [5]	10 790	APTT >34 s or PT >14 s	9[b]	NS	106 min	28	PT 8	APTT
Brohi et al., 2007 [6]	208	PT, APTT, TT >1.5x ULN	17[a]	25	32 min		NS	
Chironi et al., 2007 [7]	88	INR >1.6 or APTT >60 s or platelets <100x10^9/l or Fg <1g/l	22[b]	NS	'On admission'		28	
Maegele et al., 2007 [8]	8724	Quick's <70% or platelets <100x10^9/l	24[b]	4	69 min to admission		34.2	
Niles et al., 2008 [9]	391	INR ≥1.5	17[a]	92	'On admission'		38	
Frith et al., 2010 [10]	3646	PTr >1.2	22[a]	10	60 min to admission		36	
Floccard et al., 2010 [11]	45	ISTH DIC score ≥1	25[b]	0	25 min		56	
Davenport et al., 2011 [12]	300	ROTEM EXTEM CA5 ≤35 mm	12[a]	21	77 min	8	PT 23	CA5

The ISTH DIC uses a five-step diagnostic algorithm to calculate a coagulopathy score. Parameters included in the calculation include platelet count, fibrinogen, PT and FDP levels. Points are assigned to each laboratory parameter and a final score is determined.
NS, not stated.
[a]Median.
[b]Mean.
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INJURY-RELATED FACTORS CONTRIBUTING TO ACUTE TRAUMATIC COAGULOPATHY

The following may occur to varying degrees in each individual, predisposing to or amplifying ATC.

Consumption and loss

Coagulation factors and platelets are consumed during the formation of clots, as well as lost from the intravascular compartment during bleeding. Anaemia due to red cell loss has a major effect on primary haemostasis through reduction of axial blood flow and thus reduction of platelet and plasma margination to blood vessel walls and sites of injury [28], such that there is an inverse correlation between the haematocrit and in-vitro bleeding time [29].

Dilution

Autodilution results from reversal of Starling forces and consequent shifts of interstitial fluid into the vascular compartment. Dilution is aggravated by replacement of lost whole blood with crystalloid, colloid and red cell transfusion. The volume of fluid administered both *in vitro* and *in vivo* is proportional to the resultant coagulopathy [8,30].

Hormonal and cytokine-induced changes

Following tissue injury, levels of cytokines and hormones, such as adrenaline and vasopressin, rise, and cytokine, hormone and thrombin production lead to endothelial cell activation (ECA) [31]. Vasopressin stimulates production of tissue plasminogen activator (t-PA) and Weibel Palade body release, which increases von Willebrand factor levels and expression of P-selectin on the endothelium, enhancing platelet recruitment. Cytokines, such as TNF and IL-1, as well as thrombin and continued hypoxia, cause ECA and effect a slow change in endothelial cell phenotype from antithrombotic to prothrombotic, which in inadequately resuscitated patients leads to DIC. ECA downregulates thrombomodulin and fibrinolysis (PAI-1 levels increase), causes cleavage of glycosaminoglycans from the cell surface, limiting activation of antithrombin, increases platelet-activating factor production, increases endothelial permeability and *in vitro* upregulates the expression of tissue factor (TF) [31,32].

Hypoxia, acidosis and hypothermia

This triad predisposes to bleeding by impairing the function of platelets and coagulation proteases while increasing fibrinolysis [33]. Hypoxia exacerbates ECA and coagulopathic changes are most pronounced once pH is less than 7.1 [34] and temperatures less than 33°C [35].

Immune system activation

Tissue damage and shock are associated with platelet release of soluble CD40 ligand, a potent immune activator [36■]. Immune stimulation, including complement activation, is associated with release of damage-associated molecular patterns, such as mitochondrial damage-associated molecular patterns and histone-complexed DNA [37,38■]. Immune activation can aggravate tissue damage through mechanisms including proteolytic degradation and oxidative stress, thus amplifying coagulation activation.

CHARACTERIZATION OF ACUTE TRAUMATIC COAGULOPATHY

In two large observational studies, one-quarter of trauma patients had prolongation of an APTT and/or PT at admission which was independently associated with bleeding and death [3]. ATC was found in patients who received little or no intravenous fluid therapy, negating the long-held belief that iatrogenic haemodilution is the main causative factor in traumatic coagulopathy [6,10,12,39]. Fibrinolysis also appears to play an important role in contributing to traumatic coagulopathy [40,41■], as suggested by the reduction in mortality due to use of TXA in CRASH-2 [42,43].

Much of the work characterizing ATC has been based on standard plasma-based tests resulting in definitions based on abnormal APTT, PT, TT, INR or PTr, low platelet count, low fibrinogen level or an ISTH DIC score of at least 1–4 (nonovert DIC) or ≥ 5 (overt DIC) (Table 2) [3,40,44–47], including a description of the ISTH DIC score. Viscoelastic tests have been used to identify ATC [12], but there is no universally accepted assay or definition.

PATHOPHYSIOLOGY OF ACUTE TRAUMATIC COAGULOPATHY

Conceptually, it seems ATC is due to massive stimulation of coagulation and fibrinolysis by damaged tissues. Tissue damage *per se* leads to exposure of the subendothelial matrix, which contains TF, driving localized coagulation, and collagen which binds to platelet glycoprotein VI and vWF – glycoprotein Ib, causing platelet activation. In keeping with this hypothesis, reduced clotting factor and physiological anticoagulant levels (range 35–98%) [11,48,49]

Table 2. Visco elastic parameters used by different authors to define fibrinolysis

Study	TEG or ROTEM	Value used	Normal range (%)	Clinical setting	Prevalence of TEG hyperfibrinolysis (%)
Levrat et al., 2008 [44]	ROTEM	LI30 LI60	<2 <43	Trauma	6
Carroll et al., 2009 [45]	TEG	LY60	<15	Trauma	2
Kashuk et al., 2010 [40]	r TEG	LY60	<15	Trauma	18
Tauber et al., 2011 [46]	ROTEM	LI60	>85	Trauma	7.3
Ostrowski et al., 2011 [47]	TEG	Lys30	<8	Trauma	1

LI30 or LI60, percentage of maximum clot strength present at 30 or 60 min; LY60, percentage fibrinolysis after 60 min; Lys30, decrease in maximal amplitude over 30 min after the maximal amplitude has been reached; ROTEM, rotational thrombelastometry (TEM International, GmbH, Munich, Germany); r-TEG, rapid TEG; TEG, (TEG; Haemoscope Corp, Niles, Illinois, USA).
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and high thrombin-generating capacity [6,11,39, 50–52], as well as moderately reduced platelet counts [5,52] are found, that is, a consumptive coagulopathy. The most consumed coagulation factors following injury are fibrinogen and factor V [48,53], which are likely due, in part, to inactivation by activated protein C (aPC) or free plasmin [54,55], although the relative contributions of each are uncertain.

Thrombin is a central molecule in haemostasis – its generation not only converts fibrinogen to fibrin, resulting in fibrin strand formation, but it also activates platelets, leukocyctes and endothelium. Thrombin stimulates the production of t-PA from the endothelium, an effect previously known as secondary fibrinolysis. Stimulation of t-PA release from the endothelium by other factors, such as hypoxia, adrenaline and vasopressin, is known as primary fibrinolysis. High t-PA levels are reported in coagulopathic trauma patients [6,52]. In addition, when bound to the endothelial receptor thrombomodulin, thrombin activates protein C.

It has been argued that aPC is a major driver of ATC through its cleavage of factors Va and VIIIa, as well as binding of PAI-1, thereby possibly controlling fibrinolysis [12,39,54]. This mechanism is problematic for several reasons. Firstly, both platelet and plasma factor Va pools are resistant to aPC cleavage at concentrations of aPC relevant to either ATC or even pharmacologic dosing of recombinant human aPC in sepsis [56▪▪]. Furthermore, a normal platelet concentration of 200 000/mm^3 was able to eliminate aPC anticoagulant effects at suprapathophysiologic concentrations of aPC. In this study, aPC had no discernable effect on fibrinolysis in the presence or absence of platelets [56▪▪]. Secondly, PAI-1 is a potent inhibitor of aPC in the presence of the ubiquitous glycoprotein, vitronectin [57]. It has been hypothesized that the binding and inactivation of aPC by the vitronectin/PAI-1 complex could lead to PAI-1 depletion and thus promotion of fibrinolysis. This is unlikely given that PAI-1 circulates at roughly 10 times higher concentrations than aPC [58,59]. Furthermore, catalytic aPC neutralization of PAI-1 is a goal of pharmacologic manipulation, not likely a primary physiologic function of aPC [60,61]. We argue that it is the enormously increased production of t-PA, secondary to adrenaline, vasopressin and thrombin, not failure of inhibition which drives fibrinolysis during ATC.

After the immediate haemostatic effects resulting from tissue injury, further changes are orchestrated by ECA. As mentioned, thrombin and various cytokines cause ECA, as do hypoxia and hypoperfusion [62]. The importance of hypoperfusion in the pathogenesis of ATC has come from patient data [9,10,39,40,49,63,64] animal models, such as the rat trauma model [10,63] and in-vitro data [62,64]. These studies show that as shock indices increase (as measured by base deficit) the PT, PTr and INR values rise [4,10,12,61,62] and coagulation factor levels fell [10,62]. The largest of these studies ($n = 3646$) showed that ATC (PTr >1.2) was only evident with significant hypoperfusion (base deficit >6 mmol/l) combined with severe injury (ISS >15) [10].

The importance of fibrinolysis in ATC has come to the fore recently, for CRASH-2 reported a one-third reduction in bleeding mortality in trauma patients given TXA, a competitive inhibitor of plasminogen activation [42,43]. Other clinical data have shown that the degree of fibrinolysis is correlated with transfusion requirement [44] and mortality [44,65–68]. A sensitive marker of fibrinolysis is plasmin–antiplasmin complex, and levels are increased in nearly 60% of trauma patients [68]. Increased plasmin generation and fibrin products [69], such as D-dimers, [6,7,39,49,65,70] are found in bleeding trauma patients.

As time from injury increases, the prothrombotic effects of ECA gradually predominate,

especially if hypoxia and acidosis continue. This is partly mediated by release of phosphatidylserine-positive microparticles [71]; the endothelium switches from a net production of t-PA to a net production of PAI-1 [6,7,52,72]. A thrombotic coagulopathy and fibrinolytic shutdown ensues, thus probably explaining why treatment at this stage with an antifibrinolytic may worsen outcome [43].

Platelets play a central role in both primary haemostasis and the widely accepted cell-based model of coagulation. Platelets are resistant to collagen, ADP and arachidonic acid stimulation following trauma [73,74]. This platelet dysfunction, still of unclear cause, likely explains the many observations of improved outcomes associated with platelet transfusion despite platelet counts previously thought to be adequate [75–77]. Indeed, it appears that lower admission platelet count predicts mortality even within the normal range [78]. There is a suggestion that transfused platelet quality may be a determinant of trauma outcome [79].

Microparticles derived from blood and endothelial cells contribute to normal haemostasis. TF and thus fibrin incorporation into clots is dependent on the interaction between P-selectin glycoprotein ligand 1/TF-bearing microparticles from leukocytes and P-selectin on platelets adherent to damaged tissue [80]. Procoagulant microparticle production increases in trauma [81] and contributes to prothrombotic changes [82].

It has been argued by some that the initial picture seen in ATC is due to DIC [52,83]. However, although the early coagulation screen changes of ATC may resemble DIC resulting in a positive ISTH DIC score, there is no evidence of inappropriate disseminated clot formation on histological examination [84] – clot formation occurs only at the site of injury, so by definition early ATC is not DIC.

THE CLINICAL IMPORTANCE OF IDENTIFYING COAGULOPATHY

The hypothesis that the extent of coagulation activation will relate to the degree by which blood is exposed to TF on damaged tissues is supported by data showing that the severely injured are more likely to have ATC [4], have haemorrhagic shock [39], require transfusion support [61] and are most at risk of worsening coagulopathy and death [3,85,86].

Prediction of coagulopathy

A variety of scoring systems have been published for adults and children with injury, which aim to predict which patients will develop severe haemorrhage and thus shift clinical management from a reactive to a proactive approach [87–92]. None of the scoring systems, however, have the sensitivity to identify all patients at risk of coagulopathy and massive blood loss; any patient with major injury should therefore be assumed to be at risk [91].

METHODS FOR ACUTE TRAUMATIC COAGULOPATHY DIAGNOSIS AND MONITORING OF HAEMOSTATIC CHANGES

Standard laboratory tests

These include PT-based assays (PT, PTr and INR), APTT and Clauss fibrinogen. The PT/INR has been suggested as the more sensitive test to the multiple coagulation factor deficiencies, and therefore a better marker of ATC [53]. The current advantages of using standard tests are that every laboratory can provide these results; they have a use in guiding plasma product administration and predicting mortality [9].

Originally, the PT and APTT tests were designed to evaluate clotting factor deficiencies, not acquired coagulopathy, and are not predictors of later bleeding in these circumstances [93]. Moreover, they do not evaluate platelet number and function, fibrinolysis, thrombin generation or the interactions between coagulation proteases and phospholipid surfaces. Furthermore, turnaround times from sampling to obtaining results from the routine laboratory may be over an hour [12]. It is for these reasons that plasma-based coagulation tests have limited value in the immediate management of ATC, but they do have a major value in longitudinal monitoring during ongoing bleeding to guide the use of appropriate blood components.

Viscoelastic tests

Increasingly, TEG and ROTEM are being used in the trauma setting [46,65,68,73]. Overall, minimally injured patients tend to have normal traces, and moderate or severe trauma may be associated with TEG changes [65,71,94]. TEG and ROTEM have a role in the assessment of severe fibrinolytic activity but are not sensitive enough to detect more limited lytic activity [69]. Increased fibrinolytic activity, when detected by viscoelastic testing, is associated with a poor prognosis. Schochl *et al.* [67] and other authors arbitrarily used the term 'hyperfibrinolysis' for lysis greater than a certain maximal amplitude on ROTEM testing (Schochl uses 15%). However, confusion has arisen with this TEG/ROTEM-associated terminology because traditionally hyperfibrinolysis describes a situation in which fibrinolytic

activity is greater than fibrin formation, clot integrity is threatened, and there is clot breakdown [45] rather than a loose term used simply to describe increased evidence of fibrinolysis (Table 2). Therefore, there is a suggestion that the term 'TEG hyperfibrinolysis' be used in relation to the TEG viscoelastic measurements [95].

There is as yet no agreed viscoelastic definition of ATC, although the changes seen include the following: increases in clotting time and clot formation time, and reduction in clot amplitude and maximal clot amplitude [12,47,63,67]. One study [12] using ROTEM reported an EXTEM CA5 (clot amplitude at 5 min) value of <36 mm as diagnostic of ATC. Another study [95] suggests that TEG or ROTEM A10 correlates best with platelet count and fibrinogen level and predicted transfusion needs. Advocates for viscoelastic testing argue that the ability to distinguish different haemostatic abnormalities provides a means of individualizing coagulation management [44,68,96]. However, there are no validated ROTEM and TEG algorithms in trauma and external quality assurance schemes are at an early stage. As with standard laboratory tests, viscoelastic tests are routinely performed at 37°C, and results will underestimate coagulation disturbances in a hypothermic patient.

CONCLUSION

Despite the many advances in our understanding of ATC in the last decade, further clinical observational studies are required to further our understanding of the pathophysiology of traumatic coagulopathy and thus inform the direction of future studies to improve haemostatic management and outcome.

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Conflicts of interest
Disclaimer: The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Army or the US Department of Defense.
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